UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,231	04/09/2002	Marie-Marthe Suner	SYN-126	5862

22847 7590 06/22/2005

SYNGENTA BIOTECHNOLOGY, INC.
PATENT DEPARTMENT
3054 CORNWALLIS ROAD
P.O. BOX 12257
RESEARCH TRIANGLE PARK, NC 27709-2257

EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,231	SUNER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,26-28,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-7,26-28,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 19 November 2004 and 04 April 2005 have been entered in full. Claims 1, 3, 5-7, and 26-28 are amended. Claims 2, 4, 8-25, and 29 are cancelled. Claims 30-31 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3, 5-7, 26-28, and 30-31 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to the declaration at pg 2 of the previous Office Action (28 June 2004) is *withdrawn* in view of the newly submitted Application Data Sheet (19 November 2004).

2. The objections to the specification at pg 3 of the previous Office Action (28 June 2004) are *withdrawn* in view of the amended abstract and title (19 November 2004).

3. The objection to claim 28 at pg 3 of the previous Office Action (28 June 2004) is *withdrawn* in view of the amended claim (19 November 2004).

4. The rejection of claim 5 under 35 U.S.C. § 101 (product of nature) as set forth at pg 3-4 of the previous Office Action (28 June 2004) is *withdrawn* in view of the amended claim (19 November 2004).

5. The rejection of claim 6 under 35 U.S.C. § 112, first paragraph (deposit rules only) as set forth pg 5-6 of the previous Office Action (28 June 2004) is *withdrawn* in view of the attorney's statement (19 November 2004).

6. The rejection of claims 1-5, 7, and 26-29 under 35 U.S.C. § 112, first paragraph (enablement) as set forth at pg 6-10 of the previous Office Action (28 June 2004) is *withdrawn in part* in view of the amended and cancelled claims (19 November 2004, 04 April 2005). Please see section on 35 U.S.C. § 112, first paragraph, below.

7. The rejection of claims 1-7 and 26-29 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pg 10-12 of the previous Office Action (28 June 2004) are *withdrawn in part* in view of the amended and cancelled claims (19 November 2004, 04 April 2005). Please see section on 35 U.S.C. § 112, first paragraph, below.

8. The rejections of claims 1-7 and 26-29 under 35 U.S.C. § 112, second paragraph, as set forth at pg 12-14 of the previous Office Action (28 June 2004) are *withdrawn in part* in view of the amended and cancelled claims (19 November 2004). Please see section on 35 U.S.C. § 112, second paragraph below.

Claim Objections

9. Claim 5 is objected to because of the following informalities:

9a. In line 2, the word "by" should be amended to recite the word "but". The word "but" was recited in the original claim set and in claim 5 of the amendment of 09 April 2002.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

10. Claims 5, 7, and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *deposited erythroid cell* which is undifferentiated but is capable of expressing a tyramine receptor under the control of a globin promoter thereof and a method of producing *the deposited cell*, does not reasonably provide enablement for an isolated

erythroid cell which is undifferentiated but which is capable of expressing proteins under the control of a globin promoter thereof and a method of producing the cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pg 1-5, 7, and 26-29 of the previous Office Action (28 June 2004).

The claims are directed to a method for detecting the interaction of a tyramine receptor with an endogenous G-protein coupled signaling cascade of an erythroid cell comprising transforming an erythroid cell with a vector comprising a sequence which encodes a tyramine receptor under the control of a globin promoter and measuring the cyclic AMP levels or the free calcium ion concentration within the cell. The claims also recite that the erythroid cell is a murine erythroleukaemia cell. The claims recite an erythroid cell which is substantially undifferentiated by which is capable of expressing proteins under the control of a globin promoter. The claims recite a method of producing the erythroid cell which comprises maintaining and growing uninduced erythroid cells in culture.

Applicant's arguments (04 April 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that with regards to the enablement rejections, a declaration from the attorney of record stating that the cell lines were deposited according to the Budapest Treaty. Applicant states that the amendments, receipts, and declaration perfect the biological deposit and overcome this rejection.

Applicant's arguments have been fully considered but are not found to be persuasive. Regarding claims 5, 7, and 30, as indicated in the previous Office Action of 28 June 2004, these

claims would be enabled if the erythroid cell is the deposited cell (e.g., deposited at the European Collection of Cell Cultures under Accession No. 99012801). However, claims 5, 7, and 30 still read upon the methods of making any undifferentiated erythroid cell and the undifferentiated cell itself. The claims are not dependent upon the deposited erythroid cell of claim 6.

The specification of the instant application does not disclose general methods of producing undifferentiated erythroid cells comprising maintaining and growing uninduced erythroid cells in culture for a sufficient period of time and isolating a subclone which expresses protein. A large quantity of experimentation would be required of one skilled in the art to determine the optimal culture conditions and necessary steps for expressing a protein in undifferentiated erythroid cells. The state of the art is such that in the conventional LCR/MEL system, heterologous receptor expression is obtained *after* DMSO-induced differentiation of the cells into mature red blood cells (Poels et al. Insect Molec Biol 10(6): 541-548, 2001). Therefore, without specific guidance, undue experimentation would be required by the skilled artisan to produce and maintain undifferentiated erythroid cells that express a protein. One skilled in the art would not be able to predict that standard art-recognized cell culturing techniques would be able to produce and maintain undifferentiated erythroid cells that express a protein. Also, the instant specification and Poels et al. indicate that the properties of the deposited cell are unexpected and have not been replicated.

11. Furthermore, claims 1 and 3 (which depend from claim 7) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for agonists of a receptor protein comprising (a) transforming the *deposited cell* with a vector comprising a sequence which encodes a tyramine receptor under the control of a globin

promoter, (b) contacting the cell with a candidate agonist, (c) measuring Ca^{2+} or cAMP levels to determine if the receptor is activated, and (d) identifying agonists as those candidates that caused a change in Ca^{2+} or cAMP levels, does not reasonably provide enablement for a method for detecting the interaction of a tyramine receptor with an endogenous G-protein coupled signaling cascade of an erythroid cell comprising transforming an erythroid cell with a vector comprising a sequence which encodes a tyramine receptor under the control of a globin promoter and measuring the cyclic AMP levels or the free calcium ion concentration within the cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pg 1-5, 7, and 26-29 of the previous Office Action (28 June 2004).

Undue experimentation would be required by the skilled artisan to produce and maintain undifferentiated erythroid cells that express a protein. One skilled in the art would not be able to predict that standard art-recognized cell culturing techniques would be able to produce and maintain undifferentiated erythroid cells that express a protein. The state of the art is such that in the conventional LCR/MEL system, heterologous receptor expression is obtained *after* DMSO-induced differentiation of the cells into mature red blood cells (Poels et al. Insect Molec Biol 10(6): 541-548, 2001). Therefore, without specific guidance, undue experimentation would be required by the skilled artisan to produce and maintain undifferentiated erythroid cells that express a protein. There is also little or no guidance in the specification as to the identities of the endogenous G-protein coupled signaling cascade and the interaction that is to be detected in the claimed assay. Undue experimentation would be required of the skilled artisan to express any

tyramine receptor under the control of a globin promoter in an undifferentiated erythroid cell and conduct all possible assays to detect an interaction between the protein and all possible signaling cascades of the cell. Such experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". The experiments disclosed in the instant specification are unrelated to the claimed method, and are therefore not adequate guidance, but merely an invitation to the artisan to use the claimed invention as a starting point for further experimentation.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to produce and maintain undifferentiated erythroid cells that express a protein, to identify a protein, an endogenous G-protein coupled signaling cascade, and the interaction between the protein and signaling cascade and to conduct all possible assays to detect the unidentified interaction, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the current state of the art (see Poels et al.), the unpredictability of producing an undifferentiated erythroid cell that expresses a protein under the control of a globin promoter, and the breadth of the claims which fail to recite limitations as to the specific erythroid cell and the production and maintenance of undifferentiated erythroid cells that express a protein as well as limitations as to the identity of the protein, signaling cascade,

and interaction detected, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

11. Claims 1, 3, 5, 7, 26-28, and 30-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this written description requirement was set forth for claims 1-7 and 26-29 at pg 10-12 of the previous Office Action (28 June 2004).

The claims are directed to a method for detecting the interaction of a tyramine receptor with an endogenous G-protein coupled signaling cascade of an erythroid cell comprising transforming an erythroid cell with a vector comprising a sequence which encodes a tyramine receptor under the control of a globin promoter and measuring the cyclic AMP levels or the free calcium ion concentration within the cell. The claims also recite the that the erythroid cell is a murine erythroleukaemia cell. The claims recite an erythroid cell which is substantially undifferentiated by which is capable of expressing proteins under the control of a globin promoter. The claims recite a method of producing the erythroid cell which comprises maintaining and growing uninduced erythroid cells in culture. The claims recite a method for detecting the interaction of a tyramine receptor with an endogenous signaling cascade of an erythroid cell comprising measuring the expression levels of the β-galactosidase gene.

Applicant's arguments (04 April 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that claim 1 has been amended to recite a particular receptor, the tyramine receptor, and a G-protein coupled signaling cascade, which are monitored by measuring the cAMP and calcium ion concentrations with the cells.

Applicant's arguments have been full considered but are not found to be persuasive. The specification of the instant specification teaches that "use can be made of the signalling pathways in the cell, such as those in which G-proteins are involved, where for example, globin promoters can drive the expression of heterologous proteins which normally functionally interact with a G-protein, in particular G-protein coupled receptor molecules (GPCR)" (pg 4, lines 13-16). The specification also teaches that cells of the invention can be used to express heterologous proteins, including human proteins and non-mammalian proteins, such as insect proteins (pg 7, lines 4-6). However, the brief description in the specification is not adequate written description of an entire genus of proteins (claims 5, 7, 30), insect G-protein coupled receptors (claims 26-28), and G-protein coupled signaling cascades or endogenous signaling cascades (claims 1, 3, 31).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of proteins, insect G-protein coupled receptors, and G-protein coupled signaling cascades or endogenous signaling cascades. (It is noted that relevant literature teaches "different GPC receptors use the same basic mechanism to act on a

wide variety of signal transduction pathways, including adenyl cyclase, tyrosine kinase cascades, and phospholipases" (Uings et al. J Clin Pathol Mol Pathol 53: 295-299, 2000; pg 298, 1st full paragraph). The state of the art also discloses that GPCRs activate multiple signal transduction pathways that act in a synergistic and combinatorial fashion. For example, numerous signal transduction pathways are activated by engagement of the bombesin/GRP receptor (Rozengurt, E. J Cell Physiol 177: 507-517, 1998; pg 508-509, Figures 1-2).)

35 USC § 112, second paragraph

12. Claims 1, 3, 5-7, and 30-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. The term "interaction" in claims 1, 3, and 31 is a relative term which renders the claims indefinite. The term "interaction" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, what interaction is occurring between a heterologous protein and an endogenous signaling cascade? Binding? Activation? Inactivation? The basis for this rejection is set forth for claims 1-4 at pg 13 of the previous Office Action (28 June 2004).

Applicant's arguments (19 November 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that those of ordinary skill in the art would understand the meaning of the term and that it refers to any number of ways a protein can interact with an endogenous

signaling cascade. Applicant's arguments have been fully considered but are not found to be persuasive. As indicated in the previous Office Action, one of skill in the art would not know the metes and bounds of the encompassed "interactions". Applicant even states that the term refers to "any number of ways a protein can interact with an endogenous signaling cascade".

14. Claims 1, 3, 31 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the assay steps that detect the protein interaction with an endogenous signaling cascade. The basis for this rejection is set forth for claims 1-4 at pg 13 of the previous Office Action (28 June 2004).

Applicant's arguments (19 November 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons. Although Applicant indicates that the claims have been amended to specify the steps that detect protein interaction with an endogenous signaling cascade, one critical step still seems to missing from the claims. Specifically, the receptor has to be activated in order to measure cAMP, free calcium ion concentration, or levels of the β-galactosidase gene. The specification of the instant application even discloses that "the G-protein coupled receptor signal is induced in the presence of ligands for that receptor" (pg 4, lines 28-29).

15. Claims 1, 3, 5, 6, 7, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the uninduced/undifferentiated erythroid cells are maintained and grown in culture. For example, what media is used? What temperature?

What growth factors are/are not used? How much time cultured? The basis for this rejection is set forth for claim 7 at pg 14 of the previous Office Action (28 June 2004).

Applicant's arguments (19 November 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons. Applicant contends that claim 7 has been amended to more clearly specify the essential steps. However, the claim still does not recite any steps indicating how the undifferentiated erythroid cell is generated. The claim was only amended to further limit the erythroid cell itself. One skilled in the art would not know the metes and bounds of the encompassed method.

16. Claims 1 and 3 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating how measuring cAMP levels or free calcium ion concentration within the cell detects the interaction of a tyramine receptor with a G-protein coupled signaling cascade. There is no nexus between cAMP levels or free calcium ion concentration and detection of the interaction of a tyramine receptor with a G-protein coupled signaling cascade.

17. Claim 31 recites the limitation "a tyramine receptor" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 31 depends from claims 27 and 28, which do not recite an erythroid cell that expresses a tyramine receptor. Claims 27 and 28 depend from claim 26 which recites that an erythroid cell is transformed with a vector comprising a sequence which encodes *an insect G-protein coupled receptor*. Claim 26 does not specifically recite a tyramine receptor.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
15 June 2005

ELIZABETH KEMMERER
PRIMARY EXAMINER